REMARKS

The Office Action dated September 26, 2003 has been received and carefully studied.

The Examiner states that the Information Disclosure Statement filed September 9, 2001 fails to comply with the rules.

Firstly, no IDS was filed on September 9, 2001. The only IDS filed in this case was mailed September 14, 2001. Secondly, the IDS was accompanied by Form PTO-1449, which correctly listed all patents and publications cited. Thirdly, copies of all cited references were provided. Submitted herewith is the return postcard, stamped by the PTO, indicating receipt of all of the above on September 17, 2001. Also submitted herewith is another copy of the IDS and Form PTO-1449 for the convenience of the Examiner. Consideration thereof is respectfully requested.

The Examiner rejects claims 6 and 11-16 under 35 U.S.C. 102(b) as being anticipated by Johansson et al., U.S. Patent No. 5,559,269 and U.S. Patent No. 5,686,464.

The rejections are respectfully traversed.

Background of the invention

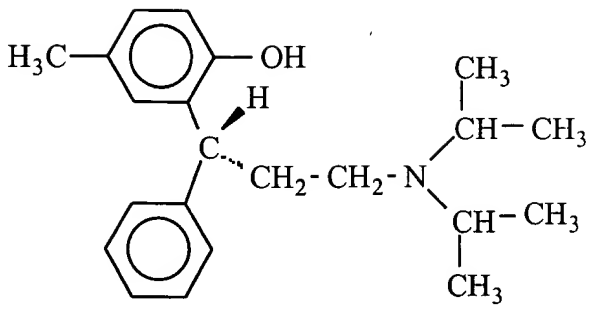
An estimated 17 million people in the USA suffer from urinary urge incontinence. This corresponds to an estimated 50 million people worldwide. Two anticholinergic drugs dominate the market: oxybutynin (Ditropan®, ALZA/J&J) and tolterodine (Detrol®, Pharmacia/Pfizer). A third drug,

terodiline (Micturine®, Kabi) was withdrawn from the market several years ago, since it was found to cause a fatal type of cardiac arrhythmias that is called Torsades de Pointes. Such arrhythmias are caused by inhibition of a repolarizing current in the heart (the ``delayed rectifier'') and can be observed as a prolongation of the QTc-segment of the ECG. A therapeutic crisis is presently developing since both oxybutynin and tolterodine have recently been found to cause the same type of QTc-prolongation that forced the withdrawal of terodiline. The anticipated withdrawal of the two remaining drugs for urinary urge incontinence may prove disastrous for all the patients who are depending on these two drugs, unless effective, non-arrhythmogenic drugs for urinary urge incontinence can be invented and introduced. A race is therefore ongoing in the pharmaceutical industry to find replacement therapy for oxybutynin and tolterodine.

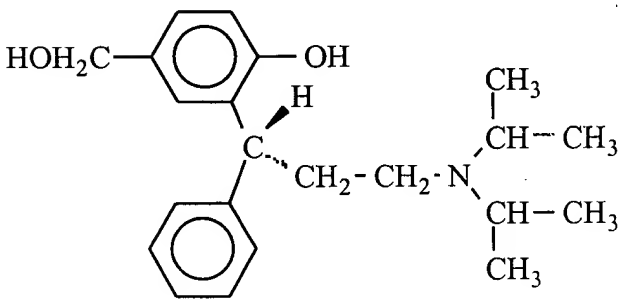
The present inventor has unexpectedly found that a metabolite of tolterodine, R(+)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (DES-TOLT) that previously was believed to be therapeutically inactive, actually potently inhibits the involuntary contractions of the urinary bladder that cause urinary urge incontinence. Furthermore, the present inventor has found this metabolite to be free from prolongation of the QTc interval of the ECG. Another major metabolite of tolterodine, R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine (5-HM or 5HM-TOLT) is already known to

have therapeutic activity (Johansson et al.). However, there were no reasons to believe that a single oxidation of the 5-Me position should change any of the pharmacological side effects or the toxicological characteristics of tolterodine and there has therefore been no incentive to develop 5-HM into a drug after it was disclosed in USP `269 by Johansson. However, the present inventor has unexpectedly found that 5HM-TOLT is free from the much-feared side effect of QTc-prolongation. This is nowhere disclosed or suggested by the Johansson et al. (USP 5,559,269 and 5,686,464) or in other prior art known to the inventor. Thus, unexpectedly, both DES-TOLT and 5-HM-TOLT will be useful as non-arrhythmogenic replacement therapy for TOLT.

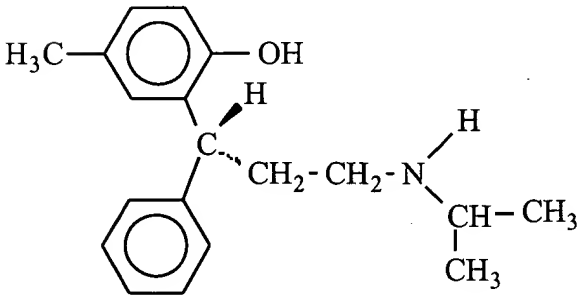
The chemical structures of tolterodine and the tolterodine metabolites DES-TOLT and 5-HM (also called 5-HM-TOLT) are shown on page 5 for the convenience of the Examiner.



R(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine
Tolterodine (**TOLT**)



R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-
3-phenylpropylamine **5-hydroxymethyl-tolterodine** (**5-HM**)



R(+)-N-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine
Des-isopropyl-tolterodine (**DES-TOLT**)

The Examiner rejects claims 1, 4, 5, 6, and 9-17 under 35 U.S.C. §103(a) as being unpatentable over Johansson et al. `464. The Examiner considers the compounds recited in these claims to be structural analogs of the Johansson et al. compounds, and believes that the skilled artisan would be motivated to select the claimed compounds with the expectation that substitution of a methyl group for a hydrogen atom would not significantly alter the analogous properties due to the close structural similarity.

The Examiner also rejects claims 1-17 under 35 U.S.C. §103(a) as being unpatentable over Johansson et al. `132 for similar reasons.

By the accompanying amendment, claims 1-3 have been amended by limiting the compounds recited therein to RS-des-tolterodine, R(+)-des-tolterodine, 5-HM-tolterodine and RS-5-HM-tolterodine. Claims 4 and 5 have been cancelled. In addition, claim 6 has been amended by eliminating RS-N-isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine (RS-des-5-HM-Des-tolterodine), and R(+)-N-isopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenylpropylamine (R(+)-des-5-HM-Des-tolterodine). Claims 9 and 10 have been canceled.

The two compounds of the invention

The present patent application concerns the therapeutic usefulness of two different metabolites that are formed in the liver from tolterodine (TOLT). TOLT is an R-

isomer and the corresponding racemate is here called RS-TOLT.

The first metabolite is:

5-HM, which is the 5-hydroxymethyl metabolite of TOLT, and which chemically is R(+)-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxy methyl)phenyl)-3-phenylpropylamine and **RS-5-HM**, which is the 5-hydroxymethyl metabolite of RS-TOLT, and which chemically is RS-N,N-diisopropyl-3-(2-hydroxy-5-(hydroxymethyl)phenyl)-3-phenyl propylamine. This metabolite of TOLT was described by Johansson et al in US Patents 5,559,269 and 5,686,464, but was not developed since it did not offer any therapeutic advantages over tolterodine.

The second metabolite is:

DES-TOLT, which is a secondary amine metabolite of TOLT, and which chemically is called R(+)-N-Isopropyl-3-(2-hydroxy-5-methyl phenyl)-3-phenylpropylamine and **RS-DES-TOLT**, which is the secondary amine metabolite of RS-TOLT, and which is called RS-N-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine. This metabolite of TOLT does not have antimuscarinic activity, but has nevertheless now surprisingly been found by the present inventor to be pharmacologically active and to potently inhibit contractions of hyperactive smooth muscle in vivo. The mechanism of the therapeutic action of DES-TOLT is not known,

but there are several possibilities, including potassium channel activation, calcium channel inhibition, interaction with serotonin and numerous other mechanisms.

Replacement for current therapy

There has not been any incentive to develop any of said two metabolites into a new drug, since no advantages over the present therapy have been identified (the present therapy being TOLT = tolterodine = Detrol®, Pharmacia.) Since the incontinence drug TOLT has recently been found to cause prolongation of the QTc segment of the ECG and since QTc-prolongation is the most common cause of a fatal cardiac arrhythmia, called Torsades de pointes, much work is presently being directed to finding replacement therapy for TOLT. The replacement for TOLT must cause relaxation of smooth muscle in vivo and must not cause any prolongation of QTc. The severity of the side effect called ``Torsades de pointes'' is obvious from the fact that another incontinence drug (terodiline, Micturin®) as well as an antihistamine (terfenadine, Seldane®) and several other drugs, such as for example astemizole (Hismanal®), have been withdrawn from the market by regulatory authorities worldwide because these drugs caused prolongation of QTc. It is now feared and anticipated that the incontinence drug TOLT may be withdrawn from the market by the FDA and its international regulatory counterparts. Interestingly and importantly, the present inventor has found that the two therapeutically active metabolites of tolterodine (DES-TOLT and

5-HM-TOLT) do not cause QTc-prolongation. Thus, the arrhythmogenic activity of TOLT resides in the parent compound (tolterodine ``itself'').

The attached declaration

A. ``Therapeutic activities''

Submitted herewith is a Declaration from Dr. Gunnar Aberg, the inventor of the present invention. In the Aberg Declaration, previously known results using tolterodine and the 5-hydroxymethyl metabolite of tolterodine in antimuscarinic testing were confirmed. Thus 5-HM tolterodine is somewhat more active as an antimuscarinic agent than tolterodine, which is not of major therapeutic importance in this case, since therapeutic doses of tolterodine are just a few milligrams. Des-tolterodine had practically no antimuscarinic activity, which presumably has led other scientists to the previously prevailing conclusion that this compound (DES-TOLT) is therapeutically inactive.

Thus, while smooth muscle relaxation of urinary bladders in vivo with 5-HM-TOLT could be expected from the receptor binding studies and the functional antimuscarinic results, the positive in vivo results with DES-TOLT were unexpected.

B. Cardiovascular Side Effects (QTc)

The present *in vivo* studies confirm the *in vitro* results of the Dalhousie group (Jones et al. Br. J. Pharmacol 2000, 131: 245-254) who found similar effects of terodiline and oxybutynin on action potential duration (which is seen as QT interval on the

ECG; since QT is partly dependent on heart rate (HR), the HR-corrected value is called QTc). Tolterodine prolonged QTc even more potently than oxybutynin or terodiline in the *in vivo* studies by the present inventor.

The secondary amine metabolite of tolterodine (DES-TOLT) and the 5-hydroxy-methyl metabolite (5-HM-TOLT) did not prolong the QTc interval *in vivo*.

It was surprisingly found that the secondary amine metabolite of tolterodine caused relaxation of the urinary bladder in vivo. This was totally unexpected since DES-TOLT does not express antimuscarinic activities in receptor binding tests or in functional anti-muscarinic studies. Previous compounds of this class do not cause relief of urinary incontinence unless they have antimuscarinic activity.

A remarkable finding was that - contrary to tolterodine - both active metabolites of tolterodine (DES-TOLT and 5-HM-TOLT) were completely free from all effects on the QTc-interval of the ECG. It is therefore concluded that the increase in duration of the QTc-interval after administration of tolterodine is exclusively caused by the parent compound (tolterodine ``itself'') and this activity is not residing in any of the two active metabolites. It is certainly unexpected that the 5-HM metabolite does not cause QTc-prolongation since there is only a very minor difference in chemical structure between 5-hydroxymethyl-tolterodine and tolterodine (that has a methyl group in this 5-position. In light of the

fact that the severely arrhythmogenic drug terodiline is a secondary amine, it was also unexpected that the secondary amine metabolite (DES-TOLT) of tolterodine proved to be free from the much feared side effect of QTc-prolongation.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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